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60/180.326 4 February 2000 (04.02.2000) US patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
0016346.9 3 July 2000 (03.07.2000) GB IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
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Road, Cambridge CB2 2QH (GB). For two-letter codes and other abbreviations, refer to the "Guid-
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(54) Title: COMBINATORIAL PROTEIN DOMAINS

(57) Abstract: The present invention relates to a chimaeric folded protein domain comprising two or more sequence segments from parent amino acid sequences that are not homologous, wherein each of said sequence segments: is not designed or selected to consist solely of a single complete protein structural element and is not designed or selected to consist solely of an entire protein domain; and, in isolation, shows no significant folding at the melting temperature of the chimaeric protein; as well as to methods for the selection of such domains; and to a chimaeric folded protein domain comprising two or more sequence segments which share common sequences or sequences from common regions in the protein fold of their parent amino acid sequences, wherein the said common region of the fold is not designed or selected to consist solely of one or more complete protein structural elements, and wherein each of said sequence segments: is not designed or selected to consist solely of an entire protein domain; and wherein, in isolation, each said sequence segment shows no significant folding at the melting temperature of the chimaeric protein; as well as to methods for the selection of such domains.

INTERNATIONAL SEARCH REPORT

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4. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/62 C07K14/00 C12N15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 21914 A (PASTEUR MERIEUX SERUMS ET VACCINS) 17 August 1995 (1995-08-17) the whole document ---	28-34, 66-72
X	WO 97 32017 A (MORPHOSIS GMBH) 4 September 1997 (1997-09-04) the whole document ---	28-34, 66-72
A	WO 99 58655 A (MEDICAL RESEARCH COUNCIL) 18 November 1999 (1999-11-18) the whole document --- -/--	28-34, 66-72

☒ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex

* Special categories of cited documents

- 'A' document defining the general state of the art which is not considered to be of particular relevance
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- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- 'Y' document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	P J O'BRIEN & D HERSCHLAG: "Catalytic	1-79
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	US	
X	<p>---</p> <p>M FLAJOLET ET AL.: "A genomic approach of the hepatitis C virus generates a protein interaction map"</p> <p>GENE.,</p> <p>vol. 242, no. 2, January 2000 (2000-01), pages 369-379, XP002178862</p> <p>ELSEVIER BIOMEDICAL PRESS. AMSTERDAM., NL</p> <p>ISSN: 0378-1119</p> <p>the whole document</p>	1-27
A	<p>---</p> <p>M OSTERMEIER ET AL.: "Combinatorial protein engineering by incremental truncation"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA.,</p> <p>vol. 96, March 1999 (1999-03), pages 3562-3567, XP002178863</p> <p>NATIONAL ACADEMY OF SCIENCE. WASHINGTON., US</p> <p>ISSN: 0027-8424</p> <p>cited in the application</p> <p>the whole document</p>	1-27
P,X	<p>---</p> <p>M M ALTAMIRANO ET AL.: "Directed evolution of new catalytic activity using the alpha-beta-barrel scaffold"</p> <p>NATURE.,</p> <p>vol. 403, 10 February 2000 (2000-02-10), pages 617-622, XP002178864</p> <p>MACMILLAN MAGAZINES., US</p> <p>ISSN: 0028-0836</p> <p>cited in the application</p> <p>the whole document</p> <p>---</p> <p>-/--</p>	1-27

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/GB 01/00445

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	<p>A CRAMER ET AL.: "DNA shuffling of a family of genes from diverse species accelerates directed evolution"</p> <p>NATURE, ,</p> <p>vol. 391, 15 January 1998 (1998-01-15), pages 288-291, XP002178865</p> <p>MACMILLAN MAGAZINES., US</p> <p>ISSN: 0028-0836</p> <p>cited in the application</p> <p>the whole document</p> <p>---</p>	1-27
P, X	<p>L RIECHMANN & G WINTER: "Novel folded protein domains generated by combinatorial shuffling of polypeptide segments"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA.,</p> <p>vol. 97, no. 18,</p> <p>29 August 2000 (2000-08-29), pages 10068-10073, XP002178866</p> <p>NATIONAL ACADEMY OF SCIENCE. WASHINGTON., US</p> <p>ISSN: 0027-8424</p> <p>the whole document</p> <p>---</p> <p>WO 01 42432 A (MRC)</p> <p>14 June 2001 (2001-06-14)</p> <p>the whole document</p> <p>-----</p>	1-78
		1-27